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EFFECTS OF COCAINE ON SIMPLE REACTION TIMES AND SENSORY THRESHOLDS IN BABOONS

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The effects of chronic, daily administration of cocaine on auditory and visual reaction times and thresholds were studied in baboons. Single intramuscular injections of cocaine hydrochloride (0.1 to 5.6 mg/kg) were given once daily for periods of 10 to 25 days, and were followed immediately by psychophysical tests designed to assess cocaine's effects on simple reaction times as well as on auditory and visual threshold functions. Consistent reductions in reaction times were frequently observed over the cocaine dose range of 0.32 to 1.0 mg/kg; at higher doses, either decreases or increases in reaction times were observed, depending upon the animal. Lowered reaction times generally occurred immediately following the 1st day's cocaine injection, and continued through all subsequent days during the dose administration period, suggesting little development of tolerance or sensitivity to these reaction-time effects. Reaction-time decreases showed a U-shaped dose-effect function. The greatest decreases in reaction times occurred from 0.32 to 1.0 mg/kg, and produced an average reaction-time decrease of 10 to 12%. Concurrently measured auditory and visual thresholds showed no systematic changes as a function of cocaine dose. Pausing was observed during performance of the psychophysical tasks, with the length of total session pause times being directly related to cocaine dose.

Key words: cocaine, reaction time, auditory threshold, visual threshold, lever press, baboons

Among users of cocaine, the view that this psychomotor stimulant can enhance one's behavioral performances is widespread. Enhancements have been described in anecdotal reports by cocaine users and chewers, but these effects have rarely been tested experimentally (Fischman, 1984), and the few experimental studies examining cocaine's effects in humans have not supported these reports (Fischman, 1984; Johanson, 1984). Cocaine does not affect, for example, hand-grip strength (Resnick, Kestenbaum, & Schwartz, 1980) or reaction times in rested subjects (Fischman & Schuster, 1980). When subjects are deprived of sleep, however, cocaine does reverse the deprivation-induced decrements in reaction times (Fischman & Schuster, 1980). This effect parallels that reported for amphetamines in returning fatigue-induced performance decrements to normal while having minimal effects on normal performances (Kornetsky, Mirsky, Kessler, & Dorff, 1959; Weiss & Laties, 1962).

Little research exists on the performance effects of cocaine in nonhuman animals. Given acutely, cocaine can produce dose-related decreases in reaction times in nonhuman primates responding to visual and auditory stimuli (Hienz, Spear, Brady, & Bowers, 1993). More generally, cocaine and other stimulants are known to increase the frequency of general motor behavior in many species, especially repetitive stereotypic movements (Bauer & Fuster, 1978; Kilbey & Ellinwood, 1977; Koek & Slangen, 1984; Ljunberg & Enquist, 1987; Post & Rose, 1976; Ridley, Baker, Owen, Cross, & Crow, 1982; Stripling & Ellinwood, 1977). Monkeys, for example, experience restlessness, heightened activity, and increased sensitivity to environmental change following 3.0 mg/kg cocaine (Wilson, Bedford, Buelke, & Kibbe, 1976). Cocaine's ability to modify operant response rates under many reinforcement schedules is also well documented (see Goldberg, Kelleher, & Goldberg, 1981), as is the rate dependency of such effects (cf. Johanson & Fischman, 1989). Relatedly, other stimulants such as amphetamines have been shown to increase the endurance of animals performing operant tasks such as swimming or treadmill running (Laties & Weiss, 1981). And *d*-methamphetamine has also been shown to decrease reaction times in a dose-related fashion in nonhuman primates performing a reaction-time task (Hienz, Lukas, & Brady, 1985).

The present report describes the effects of daily cocaine administration on auditory and visual reaction-time performances in baboons. The behavioral procedures employed also per-

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mitted independent evaluation of cocaine's concurrent effects on measures of sensory thresholds for acoustic and visual stimuli, and the use of daily cocaine dosing permitted an evaluation of whether tolerance and/or sensitivity would develop to any observed changes in reaction times or sensory thresholds.

METHOD

Subjects

The subjects were 4 male drug-naive dog-faced baboons (*Papio anubis* and *cynocephalus* subtypes), housed in individual cages and maintained on a 22-hr restricted feeding schedule with supplemental monkey chow and fresh fruit provided on a daily basis after each experimental session. The feeding schedule permitted progressive weight gain, although at 5 to 10% below ad libitum weights. Water was freely available at all times in the home cage. The general health and appearance of each animal were checked daily. Detailed medical examinations, including weight checks, were conducted monthly by trained and certified animal technicians. Animal care was in accordance with current federal guidelines concerning the humane treatment of nonhuman primates. All baboons had previous experience with the experimental procedures. Baboons MU and WE had extensive drug histories, including exposures to Δ-9-tetrahydrocannabinol and opiates; Baboons AC and MU also had a previous history with acute administrations of cocaine. Baboon MO was drug-naive except for once-monthly sedation with ketamine for physical examinations.

Apparatus

All testing was conducted in a totally darkened, double-walled sound-attenuating chamber. The testing apparatus consisted of a modified baboon squeeze cage fitted within a double-walled sound-attenuating chamber (Industrial Acoustics, Model 1201-A). An intelligence panel (76 cm by 97 cm) attached to one side of the cage contained a primate lever (BRS/LVE Model PRL-003), a red light-emitting diode used as a cuelight, an opaque Plexiglas visual stimulus patch (2.5 cm diameter), and a metal food hopper for delivery of 500-mg banana-flavored pellets. The cuelight was used to signal trial initiations. With an animal positioned facing the panel, the cuelight was at eye level, and the response lever was at waist level in front of the right arm. A wide-range speaker was suspended outside the cage and was located directly over the animal's head, 20 cm above ear level; it was used for the delivery of pure-tone acoustic signals. Animals were moved from their home cages to the testing chambers via a metal transfer cage. Baboons were observed via a closed-circuit infrared TV monitoring system during test sessions.

Stimuli

Acoustic signals were 16.0-kHz pure tones that were generated by a Krohn-Hite oscillator and then passed through an electronic switch (20-ms rise/fall times), programmable attenuator, amplifier, and a wide-range speaker. The system was calibrated with a General Radio sound level meter, a Bruel and Kjaer amplifier, and a 1.25-cm condenser microphone located at ear level facing the speaker. The light source for the visual stimuli was a slide projector mounted on the outside of the chamber that projected white light onto the back of the stimulus patch through an otherwise light-tight aperture in the chamber wall. Stimulus intensity was varied by using neutral density filters in the slide projector. Light intensities were calibrated with a light meter (United Detector Technology, Model 40X). An Apple IIe® computer controlled the experiments and collected the data.

Procedure

The psychophysical methodology involved the use of a reaction-time procedure. Baboons pressed a lever and held it depressed for varying intervals until a "reaction-time" stimulus (tone burst or light flash) signaled the availability of food reward following lever release. Correct responses (lever releases occurring within 1.5 s after stimulus onset) were reinforced with banana-flavored food pellets. Detection thresholds were determined by systematically varying stimulus intensity and recording the frequency of correct and incorrect responses. Reaction times were defined as the response latencies of each correct response and were measured as the elapsed time between signal onset and lever release.

Each session consisted of hundreds of successive reaction-time trials, with the events in each trial programmed as follows: In the pres-

ence of the flashing red cuelight (five times per second), a lever press changed the flashing red light to a continuous red light, which remained steady as feedback as long as an animal held the lever down. At intervals ranging from 1.0 to 7.0 s after initiation of this maintained holding response, a stimulus (S^D) was presented for 1.5 s. This S^D was a tone burst in the auditory reaction-time procedure and a light flash in the visual reaction-time procedure. Release of the lever within the 1.5-s stimulus duration delivered the reinforcer (one 500-mg banana-flavored pellet) and initiated a 3-s intertrial interval (ITI) during which no stimuli were presented and additional lever responses reinitiated the ITI. Lever releases prior to stimulus onset produced a timeout (5 to 10 s) without reinforcement. The length of the timeout was adjusted individually for each baboon. If an animal failed to release the lever during a stimulus, the red cuelight was turned off following stimulus offset, and lever release then returned the animal to the ITI. Following the end of the ITI, the flashing red cuelight signaled initiation of the next trial in the series of several hundred that comprised each daily session. For Baboons MU and AC, dose-effect functions for all behavioral measures were initially determined while these animals performed under an auditory reaction-time procedure; dose-effect functions were then redetermined while these animals performed under a visual reaction-time procedure. Dose-effect functions were determined for Baboon WE performing on an auditory reaction-time procedure only, and for Baboon MO performing on a visual reaction-time procedure only. Baboons were also observed via the infrared camera system. On nondrug days, subjects were observed randomly for short periods of time during sessions. On drug days, subjects were generally observed during the 15-min dark adaptation period following drug injection and during the subsequent warm-up period and/or during lengthy pauses in responding. During auditory threshold testing sessions, observations were not possible when animals were performing, because high-frequency noise from the video camera interfered with the detection of near-threshold tones.

Reaction Time and Threshold Determinations

Both auditory and visual reaction times and thresholds were measured by randomly varying the intensity of the stimuli from trial to trial (method of constant stimuli) and examining lever release latencies (i.e., reaction times) and detection frequencies (i.e., percentage of correct lever releases during the S^D) at a number of different intensities. Correct detections were defined as lever releases within the 1.5-s duration of the S^D. A latency criterion for defining correct detections produces threshold estimates comparable to other psychophysical procedures if the latency criterion is 1 s or greater (Pfingst, Hienz, & Miller, 1975). For the auditory modality, four intensity levels (10 dB apart) of the 16.0-kHz pure tone were used, with the lowest level set just below an animal's estimated threshold. These intensities were approximately 25, 15, 5, and -5 dB relative to an animal's auditory threshold. For the visual modality, four intensity levels (5 dB apart) of white light were used, again with the lowest level set just below the animal's estimated threshold. These visual intensity levels were comparably selected at 12.5, 7.5, 2.5, and -2.5 dB relative to an animal's visual threshold. By standard convention, tone intensities are specified in terms of decibels of sound pressure level (SPL); for comparative purposes, light intensities are specified in terms of a corresponding decibel scale of light intensity relative to an energy level of 0.000001 millilamberts (or 3.18×10^{-6} cd/m^2, which approximates the human threshold for scotopic vision). The difference in step size for auditory versus visual stimuli is due to the use of pressure versus energy scales for auditory and visual stimuli, respectively. To measure the false alarm or "guessing" rate of animals, a series of "catch" trials were randomly interspersed ($p = .20$) among both the auditory and visual test trials. During catch trials no auditory or visual test stimuli were actually presented. Lever releases during catch trials were punished with a 5- to 10-s timeout.

Both auditory and visual test sessions occurred in a completely darkened experimental chamber, with normal testing starting after a 15-min dark adaptation period for each baboon (the cuelight used to signal trial initiations was a small, dim red light that did not appreciably affect dark adaptation). Test sessions were typically 2 hr long and were conducted 7 days per week, with each test session divided into blocks of 80 to 100 trials and each of the four intensity levels plus catch trials

presented randomly 16 to 20 times during each block. Each block of trials required about 15 to 20 min to complete, depending upon the animal. The first block of 80 to 100 trials after the 15-min adaptation period was considered a "warm-up" block, and these data were not included in the standard analyses. Thus the data for the present analyses were collected beginning at 30 to 35 min after the start of each session. Four to five subsequent blocks of trials occurred within each session, and provided for a number of within-session estimates of sensory thresholds and reaction-time functions. The highest cocaine doses resulted in lengthy periods of nonresponding. At these doses, if animals paused excessively but began to respond toward the end of the 2-hr session, session lengths were extended (e.g., to 3 hr) to measure cocaine's effects when responding resumed. Sensory thresholds were determined from the percentage of correct detections at each intensity by interpolating to the intensity that produced a detection score halfway between the false alarm rate and 100%. Reaction times were measured with millisecond resolution, and the measure of central tendency reported is the median (because reaction time distributions can be skewed due to the physiological limit on lever release times).

Performances for nondrug (saline) sessions were considered stable when (a) a session contained three or more successive threshold estimates that varied by no more than ±1.25 dB for visual thresholds and by no more than ±2 dB for auditory thresholds; (b) false alarm rates were below 30% for each block of trials within a session; (c) all successive median reaction times for the highest stimulus intensity were within 50 ms of one another for all test blocks of a session; and (d) no systematic changes occurred in either thresholds or reaction times across blocks of trials within a session. Differences in the above criteria for auditory and visual thresholds relate to the behavioral variability in sensory thresholds and the differing physical measurement units employed for auditory and visual stimuli. Prior to cocaine dosing, baselines were considered stable when 10 consecutive saline sessions met these criteria. Once daily dosing with cocaine commenced, postdrug baselines were considered stable when performances approximated predrug performance levels and met the above criteria for at least four consecutive sessions.

Data Analysis

Previous experiments showed that single injections of cocaine produce shortened reaction times that followed a specific time course over a session (Hienz et al., 1993). To distinguish the possibility of such effects in the present study, the data were examined for both increases and decreases in the reaction-time and sensory-threshold measures over the course of each individual session. Possible increases in performance measures (i.e., lengthened reaction times and/or elevated sensory thresholds) were assessed by defining the block of trials in each session for which the greatest increase occurred as the maximum or "peak" effect of the prior drug dose in, for example, elevating reaction times. Conversely, for possible decreases in these measures, the block of trials in each session for which the greatest decrease occurred was defined as the maximum effect of the prior drug dose in, for example, shortening reaction times. This analysis avoids the averaging of cocaine's effects over sessions when the drug's effects have been shown to vary (Hienz et al., 1993). The resulting maximum and minimum drug-effect values were then subtracted from mean saline-performance values to produce change scores. Identically derived maximum and minimum change scores were calculated for predrug saline control sessions for comparison purposes.

Drug Administration

Cocaine hydrochloride was administered in doses from 0.1 to 5.6 mg/kg, and included doses having no performance effects as well as those that markedly disrupted behavioral performances. Drug administration was via intramuscular (i.m.) injections in the gluteal region, given at approximately the same time every day in a single injection. Cocaine hydrochloride was diluted in 0.9% NaCl with the total concentration adjusted to yield the appropriate dose at 0.5 mL volume. The actual injection site was varied from day to day in order to avoid tissue damage from frequent injections. A single dose was typically given daily for 10 to 25 consecutive days, and was preceded and followed by a minimum of 10 consecutive days of saline control injections. Daily drug dosing was continued until performances stabilized. At low cocaine doses, daily drug administrations were stopped if an-

imals showed no behavioral effects after 10 days. At high cocaine doses, daily drug administrations were stopped if animals did not respond for 3 consecutive days or responded only sporadically for 5 to 7 days. Postdrug testing periods were extended when necessary to recover predrug performances. The higher doses of cocaine typically produced long pauses before a baboon would initiate responding, occasionally resulting in fewer trials per session and longer sessions. During these cocaine-induced initial pauses, several pellets were manually delivered at about 20-min intervals until baboons began lever pressing. For each baboon, there was a dose at which no responding occurred within 2 hr.

Reaction-Time Determinations at Higher Stimulus Intensities

Because the reaction-time procedure produces response latencies that lengthen with decreasing stimulus intensity (indicative of decreased discriminability at lower intensity levels), drug effects at different performance levels were examined by comparing reaction times across a broad range of stimulus intensities for 2 baboons. Cocaine was administered daily for 21 consecutive days, and different sets of four stimulus intensities each were presented during each session. These intensities ranged from just above sensory threshold to tone intensities of up to 100 dB SPL for Baboon MU (auditory reaction times), and to light intensities of up to 70 dB above visual threshold for Baboon MO (visual reaction times). Each stimulus intensity examined was presented during at least two sessions. Reaction times were studied following chronic cocaine administration of doses that produced clear reaction-time decreases with less intense stimuli for these 2 baboons (1.8 mg/kg for Baboon MU; 0.56 mg/kg for Baboon MO). For comparison, the same procedure was used to examine reaction times following daily saline injections as well.

RESULTS

Figure 1 summarizes the effects of cocaine on reaction times and sensory thresholds by showing individual dose–response functions for changes in reaction times for both auditory and visual stimuli and for changes in both auditory and visual thresholds. The reaction-time graphs indicate significant deviations in reaction times that are dependent upon the cocaine dose and the animal. For auditory reaction times, Baboon MU showed significant decreases in reaction times at all doses studied, whereas Baboon WE showed increased reaction times only at his highest dose (1.0 mg/kg). Baboon AC, on the other hand, showed both significant reductions in reaction times (at 0.32 mg/kg cocaine) and elevations in reaction (doses of 1.0 mg/kg and higher). Similarly, 2 of 3 baboons (MU and MO) showed significant reductions in visual reaction times following cocaine. For all animals, higher drug doses produced near-complete performance disruptions characterized by excessive pauses in responding in the procedure for up to 2 to 3 hr. Thus the reaction-time changes presented for the highest doses were generally obtained much later in the daily sessions (following these initial pauses) than reaction times for lower doses. None of the animals showed any significant changes in auditory thresholds (Figure 1). Although some individual visual threshold data points were significantly above or below baseline levels, none of the visual threshold functions showed any systematic trend as a function of cocaine dose.

As seen in Figure 1, Baboons MU and MO showed consistent decreases in visual reaction times that were greatest at doses of 1.0 and 0.42 mg/kg cocaine, respectively. Baboon AC, on the other hand, showed decreased auditory reaction times at lower doses but increased auditory reaction times at 1.0 mg/kg and higher doses. Figure 2 shows the effects of daily injections of cocaine on the total reaction-time functions of these 3 baboons for these particular doses. Shown are latency-intensity functions (median reaction times as a function of stimulus intensity) for days early, in the middle, and toward the end of their respective dosing periods, and for the first saline day following the end of the drug dosing period. For Baboons MU and MO, cocaine's maximum effect in shortening reaction times is shown by the solid lines that represent the lowest median reaction times obtained during the indicated sessions (i.e., the greatest decreases in reaction times). For Baboon AC, cocaine's maximum effect in lengthening reaction times is indicated by the solid lines in the last row of graphs, which represent the highest median reaction times obtained during

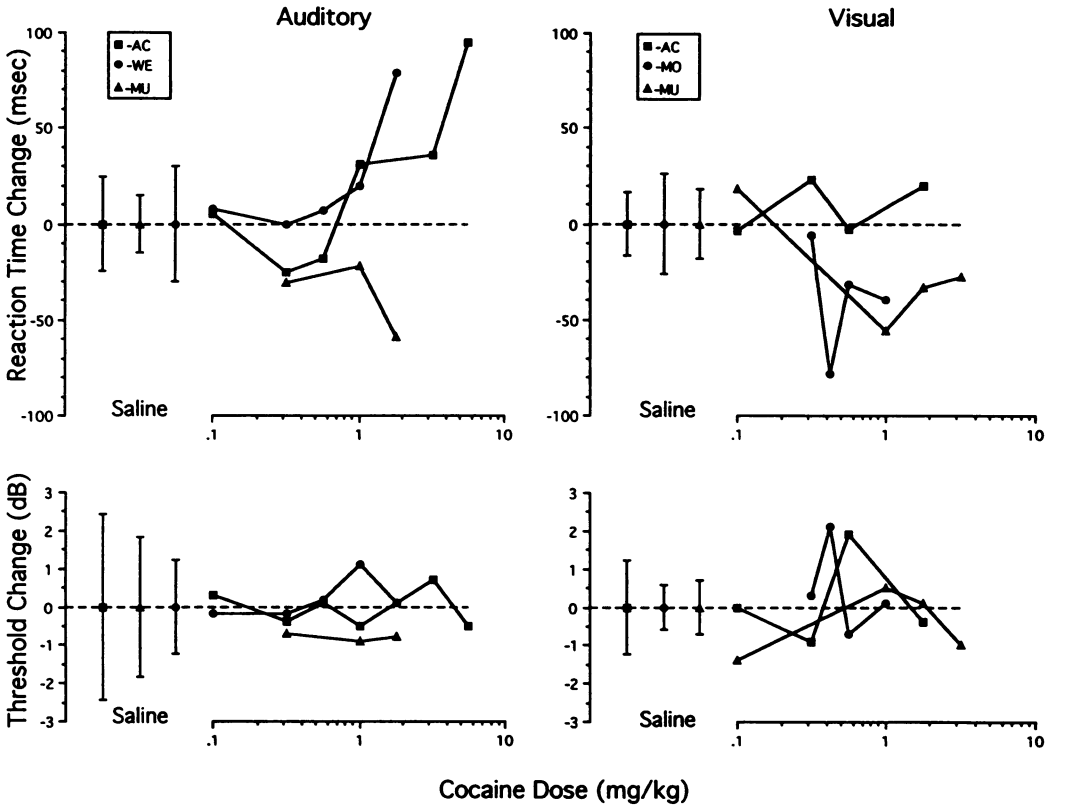

Fig. 1. Changes in auditory (left) and visual (right) reaction times (top graphs) and thresholds (bottom graphs) as a function of drug dose for individual baboons. Each point represents the mean for all sessions of the drug-dosing period. Reaction-time data are to the highest stimulus intensity only. Unconnected points indicate saline means, with error bars indicating ±1.96 *SD* (95% confidence limits).

the indicated sessions (i.e., the greatest increases in reaction times). For all baboons, all reaction-time functions showed the normal decrease in reaction times and variability as stimulus intensity increased. Following cocaine, reaction times were clearly decreased (shortened) for Baboons MU and MO. For these baboons, the lowered reaction-time functions fell outside of the 95% confidence limits for all but the lowest stimulus intensity for Baboon MU, and in many instances for Baboon MO as well. Further, these lowered reaction-time functions occurred throughout their chronic dosing periods, being just as pronounced towards the end of the chronic dosing schedule as on Day 1 (no data were available from Baboon MO on Day 1 following cocaine because the animal failed to respond during this initial session following cocaine). When daily cocaine dosing was discontinued, reaction times returned to control levels. For the lengthened reaction times of Baboon AC, clear reaction-time elevations can be seen on Day 6 following cocaine, but not at the beginning or at the end of the chronic dosing period (Figure 2, bottom row).

Figure 3 indicates how these reaction-time changes varied across the chronic dosing period by showing daily changes in reaction times across successive sessions for the 3 baboons depicted in Figure 2. Data are shown for the highest stimulus intensity only, where reaction times were shortest and day-to-day variability was minimal (as illustrated in Figure 2). For the 2 baboons showing reaction-time decreases (MU and MO, top two graphs), each point represents the difference between the lowest median reaction time within each session and the mean of all reaction times for the last 10 sessions prior to each drug dose, for both vehicle points and drug points. Occasional breaks in the function for Baboon MO indicate sessions in which excessive pausing prevented the

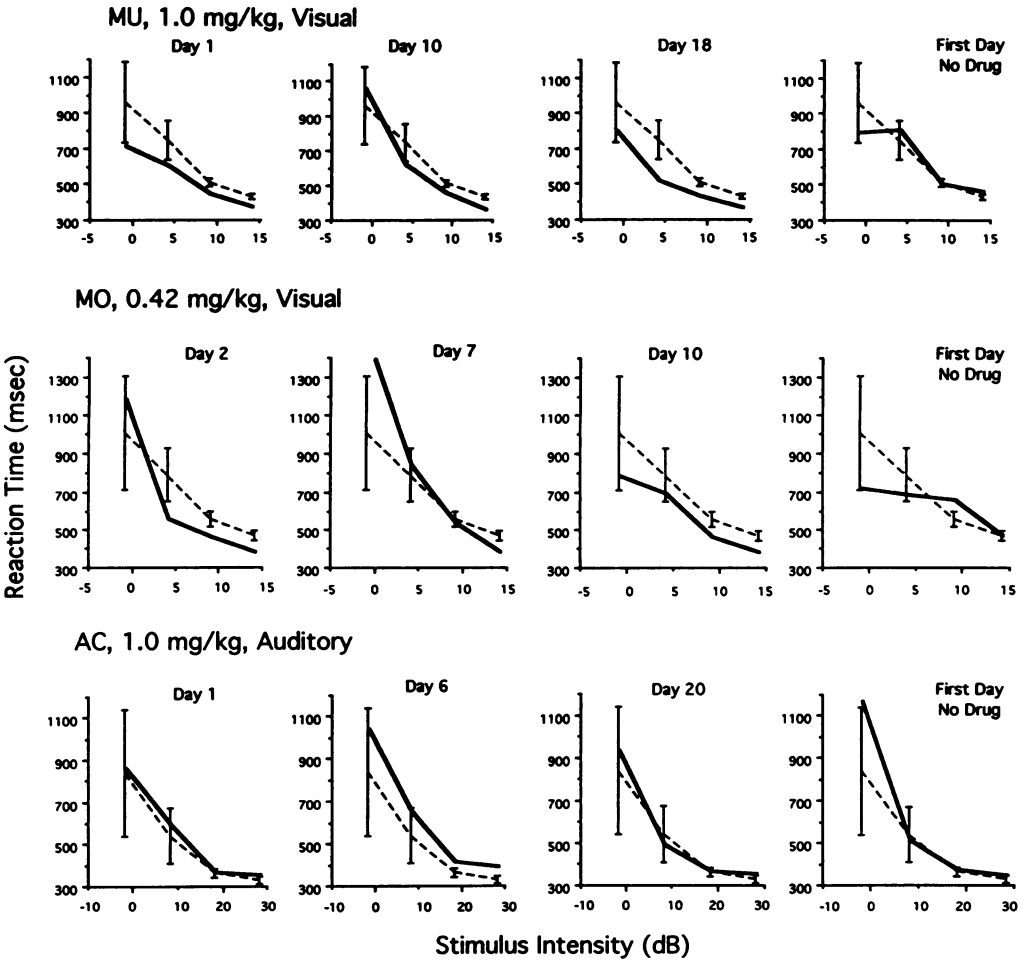

Fig. 2. Reaction times as a function of stimulus intensity for Baboons MU, MO, and AC following daily injections of the indicated cocaine doses for selected days during the chronic dosing period, and for the 1st saline day after the drug-dosing period. Dashed lines are the mean reaction time function for the 5 saline-injection days immediately preceding the 1st drug-injection day. Error bars encompass 95% confidence limits (±1.96 *SD*) about these points. Solid lines represent the lowest (for Baboons MU and MO) or the highest (for Baboon AC) reaction-time functions obtained during the indicated sessions.

collection of sufficient reaction-time data for analysis. For these 2 animals, reaction-time decreases were observed throughout the chronic dosing periods, with little indication of tolerance developing over time. Although the data for Baboon MU suggest a possible sensitivity, in that reaction times continued to decrease slightly throughout the dosing period, such an effect was not typically seen in other baboons or in this baboon at other doses. For the baboon showing reaction-time increases (AC, bottom graph), each point represents the difference between the highest median reaction time within each session and the mean of all reaction times for the last 10 sessions prior to each drug dose. Baboon AC showed sizable reaction time increases starting on the fourth day of cocaine dosing which continued through day 8 and then stabilized at a slightly lower level, suggesting the possibility that tolerance to this reaction-time-elevating effect developed over the 20-day dosing period.

Figure 4 illustrates how reaction times changed across time within individual sessions for the same animals and cocaine doses shown in Figures 2 and 3. Each graph in Figure 4 is a scatter plot of individual reaction times as a function of session time, with top, middle,

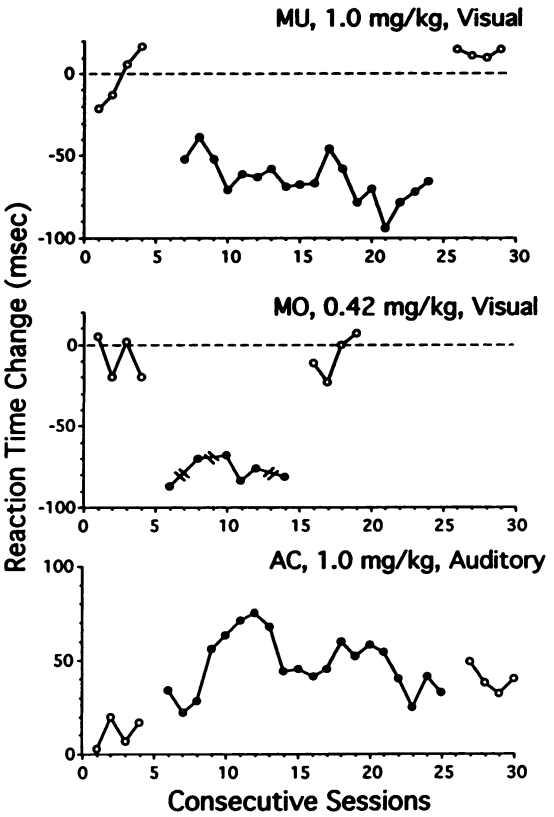

Fig. 3. Changes in reaction times at the highest stimulus intensity, shown across consecutive daily sessions following injections of either saline (open circles) or cocaine (filled circles). For Baboons MU and MO, each point represents the difference between the minimum visual reaction time for each session and the mean reaction time for the last 10 days prior to drug administration. For Baboon AC, each point represents the difference between the maximum auditory reaction time for each session and the mean reaction time for the last 10 days prior to drug administration.

and bottom graphs showing reaction times for high, medium, and low stimulus intensities, respectively, from the same session. The data for Baboon MU (left column) indicate that following 1.0 mg/kg cocaine, this animal did not respond for approximately 70 min into the session, as opposed to his normal starting time of 15 min (immediately at the end of the dark adaptation period). Following cocaine, however, Baboon MU's reaction times were decreased throughout the remainder of the session. Further, the scatter plot for this animal's reaction times at the high intensity shows little or no overlap in the distributions of reaction times following saline versus cocaine. At the medium intensity, there was greater overlap in the saline and drug reaction-time distributions, but there were clearly more shorter reaction times following cocaine compared to saline. At the low intensity, saline and drug reaction-time distributions overlapped completely; there were, however, relatively few long reaction times (i.e., >1,000 ms) at this intensity following cocaine. For Baboon MO, the 0.42-mg/kg cocaine dose disrupted his performance, producing extensive pausing at the beginning of the session, followed by a brief period of responding and then another extended period of pausing. When this animal responded, however, reaction times at the high stimulus intensity were clearly below his baseline performance level. Baboon AC (right column) paused for about 30 min into the session following 1.0 mg/kg cocaine; this animal then showed elevated reaction times for both the high and medium stimulus intensities, although the reaction-time distributions following saline and drug showed some overlap. No reaction-time differences were evident for this baboon at the low intensity.

That cocaine can shorten reaction times in the absence of changes in sensory threshold suggests that cocaine may increase stimulus "reactivity" in some manner (i.e., via an "alerting" response), in the absence of any sensory changes at or near threshold; or that these drug-induced reductions in reaction times may be a simple motor response effect. To examine these possibilities experimentally, cocaine's effects on both auditory and visual reaction times were measured across an extended range of suprathreshold stimulus intensities. Cocaine was administered daily to 2 baboons for 21 consecutive days. Figure 5 (top) shows both auditory and visual reaction times as a function of stimulus intensity for the auditory reaction times of Baboon MU following 1.8 mg/kg cocaine, and for the visual reaction times of Baboon MO following 0.56 mg/kg cocaine (the most effective doses for these animals in producing reaction-time changes without severe performance disruptions). Data are plotted on a logarithmic ordinate for better resolution at higher intensities. Clearly, chronic administration of cocaine significantly shortened both auditory and visual reaction times across a broad range of stimulus intensities. For Baboon MO, even low-intensity, near-threshold reaction times showed indications of

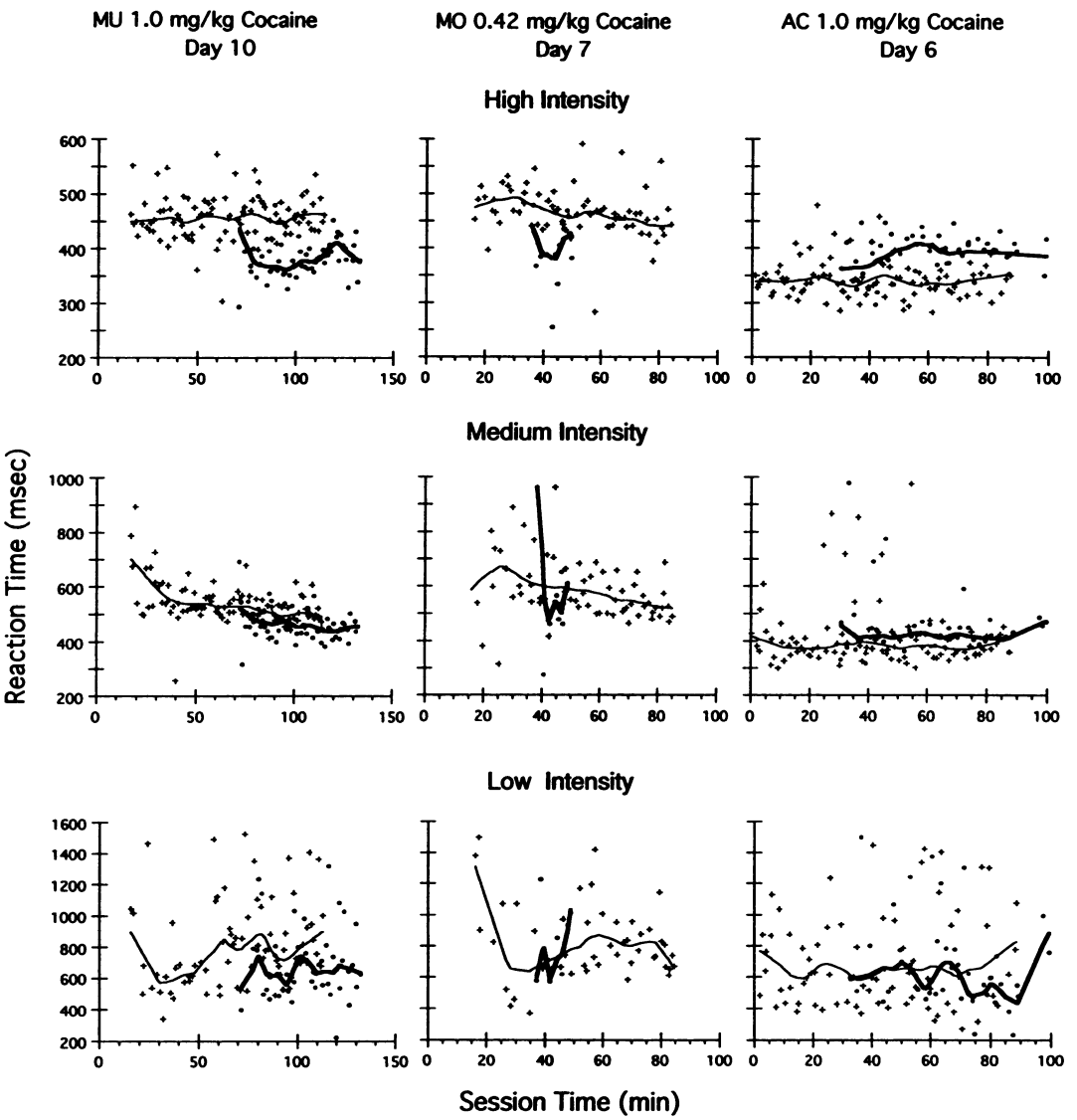

Fig. 4. Scatter plots of individual reaction times as a function of session time. Top, middle, and bottom graphs show reaction times for high, medium, and low stimulus intensities, respectively, from the same session. Data are from the last saline session and the indicated drug days taken from approximately the middle of the cocaine dosing period (+ and ● symbols, respectively). Curves in each plot are a weighted moving average of the saline and drug data points (thin and heavy lines, respectively).

being shortened following cocaine (Figure 5, top right). For Baboon MU, on the other hand, only stimuli well above auditory threshold showed the effects of cocaine (Figure 5, top left).

As plotted in Figure 5 (top), it is not readily apparent as to the degree to which reaction-time changes following cocaine were roughly equal across the intensity range. Figure 5 (bottom) shows these data replotted as percentage change in reaction times (i.e., drug latency minus saline latency, divided by saline latency) following cocaine for both Baboons MO and MU. For Baboon MO, reaction times were decreased following cocaine by a roughly proportional amount, compared to vehicle reaction times. For Baboon MU, the decreases in reaction times following cocaine were proportionally greater at higher stimulus intensities. This was due to the rather flat nature of Ba-

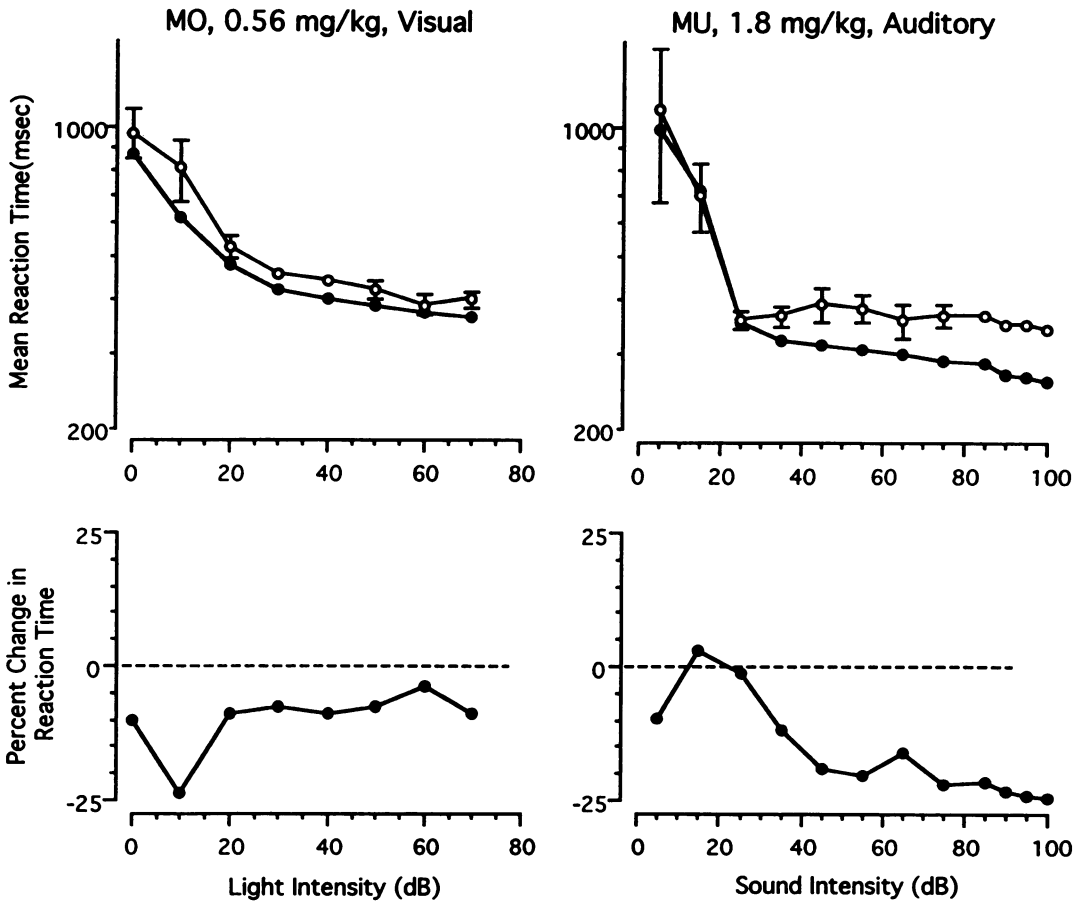

Fig. 5. Top: Reaction time as a function of stimulus intensity following cocaine (filled symbols) and saline (open symbols) for Baboons MO (top left) and MU (bottom left). Error bars indicate ±1.96 *SD* (95% confidence limits). Bottom: Same data expressed as percentage change in reaction time as a function of stimulus intensity following cocaine (filled symbols) and saline (open symbols). Each point represents the difference between a cocaine reaction time and a saline reaction time, divided by the saline reaction time and expressed as a percentage.

boon MU's nondrug reaction-time function across most of the higher intensities. Neither baboon, however, showed reaction-time decreases of an equal amount across all stimulus intensities (e.g., an x-ms decrease, regardless of stimulus intensity).

Observations of subjects via infrared cameras indicated that following low doses of cocaine, little change was seen in typical behavior except that some baboons did not initiate lever pressing as quickly at the start of the test sessions. Following high cocaine doses, however, some subjects developed repetitive, stereotypic motor patterns. One baboon engaged in right-angle head turns approximately 5 to 10 min following these higher doses, and persisted for the duration of the cocaine-induced pausing during the first part of the session. Another baboon frequently lay on the testing cage floor during the initial pause, a behavior that was not observed at other times. Other subjects showed no specific gross motor behavior changes, although lengthy pausing was still obtained with each subject at the higher cocaine doses. Response-independent pellets did not occasion responding during these periods and were generally not eaten during the pausing. The responding of all subjects was easily disrupted by loud external noises and vibrations that penetrated the sound-attenuating chambers during these sessions, whereas such noises did not disrupt responding during control sessions. Baboons showed no aberrant behavior on return to their home cages except

for an occasional lack of food acceptance. When cocaine dosing was discontinued, no abnormal behavior was observed on subsequent days, and no baboon showed shortened reaction times in the absence of cocaine.

Due to the lengthy pausing often observed following daily cocaine administration, pause times were further analyzed by plotting the percentage of each session's time during which animals paused in their performance of the psychophysical procedure. One such plot is shown in Figure 6 for the 3 baboons depicted in previous figures. The pause-time percentage was calculated by dividing the cumulative time spent not responding by the total session time and then multiplying by 100 (cumulative time spent not responding was taken as the elapsed time between the end of each ITI and the subsequent lever press initiating each trial, summed across all trials; total session time was taken as the time elapsed between the end of the dark adaptation period and the last completed trial in the session). Figure 6 shows that Baboon MU paused about 60% of the time following 1.0 mg/kg cocaine, compared to normal pause times of 15 to 20%. Baboon MO paused approximately 80 to 100% of the time following 0.42 mg/kg cocaine, and on Day 7 of drug (depicted in the scatter plots in Figure 5), this animal paused approximately 95% of the time. Baboon AC, on the other hand, showed pause-time percentages of about 40% following 1.0 mg/kg cocaine. In these particular plots, there is no evidence for changes in pause times across successive sessions, suggesting little or no development of tolerance for cocaine-induced pausing.

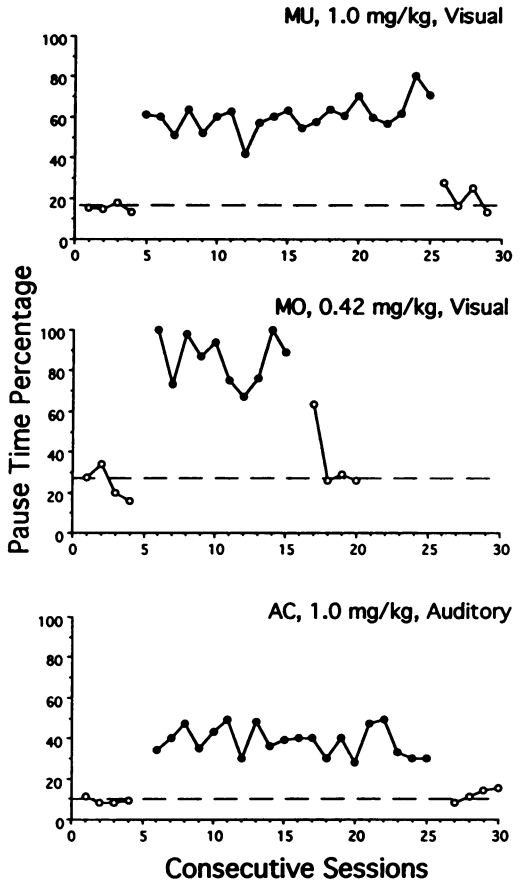

Fig. 6. Percentage of total session time not engaged in the psychophysical procedure (pause-time percentage) across successive sessions for Baboons MU, MO, and AC following injections of saline (open circles) and the indicated doses of cocaine (filled circles). Dashed lines indicate the mean value for the plotted nondrug sessions.

If one looks at pause-time percentage as a function of cocaine dose, however, such tolerance-like effects may be seen. Figure 7 shows pause-time percentages across sessions following three different cocaine doses for Baboon MU performing the auditory reaction-time procedure. For the higher doses of 1.0 and 3.2 mg/kg, this animal showed gradually decreasing pause times across successive sessions following continued cocaine dosing, suggestive of the development of tolerance. Although Baboon MU did not show this effect following his first exposure to 1.0 mg/kg cocaine under the visual reaction-time procedure (Figure 6, top graph), the data of Figure 7 were collected following Baboon MU's extensive exposure to cocaine under the visual reaction-time procedure. Further, similar indications of tolerance were seen at higher doses under the visual reaction-time procedure for Baboons MU and AC, and under the auditory reaction-time procedure for Baboon AC as well.

Figure 8 summarizes the effects of cocaine on pause time by showing dose–response functions for pause-time percentages as a function of cocaine dose, averaged across all baboons studied. Pausing increased directly as a function of cocaine dose under both the auditory and visual psychophysical procedures. Pausing increased across the dose range from 0.1 to 1.8 mg/kg, with a slight downturn occurring in the dose–response curve at 1.8 mg/kg (auditory procedure only).

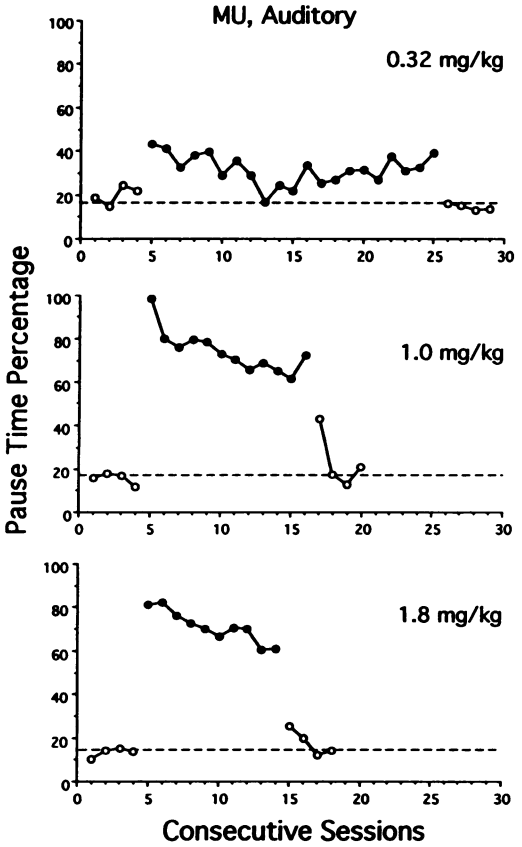

Fig. 7. Percentage of total session time not engaged in the psychophysical procedure (pause-time percentage) across successive sessions for Baboon MU following injections of saline (open circles) and the indicated doses of cocaine (filled circles). Dashed lines indicate the mean value for the plotted nondrug sessions.

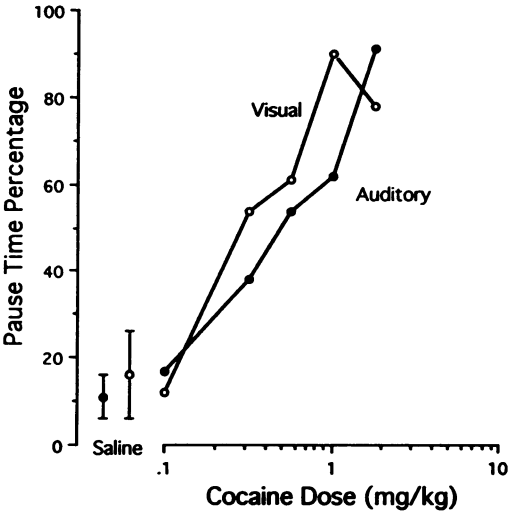

Fig. 8. Percentage of total session time not engaged in the psychophysical task (pause-time percentage) as a function of cocaine dose, averaged across all baboons. Separate functions are shown for performing under the auditory (filled circles) and visual (open circles) procedures. Error bars for the vehicle (saline) points represent ±1.96 *SD* (95% confidence limits).

DISCUSSION

The present results show that daily cocaine administration can produce a clear, significant decrease in simple reaction times. In many cases, latencies were shortened by as much as 100 ms, and neither tolerance nor sensitivity to these reaction-time-decreasing effects was observed to any great degree. Medium doses (0.32 to 1.0 mg/kg) were most effective in shortening reaction times, whereas at higher doses either shortened or lengthened reaction times were seen, depending upon the animal. Furthermore, chronic cocaine dosing generally had similar effects on both auditory and visual reaction times, suggesting that cocaine's reaction-time-shortening effects were not modality specific. In contrast to cocaine's effects on reaction times, no consistent effects of cocaine were found on either auditory or visual thresholds.

The present findings of decreased reaction times following cocaine agree with previous results of reaction-time decreases following single injections of cocaine (Hienz et al., 1993) and *d*-methamphetamine (Hienz et al., 1985) given once or twice weekly. For comparison, Figure 9 shows these previous results compared to the present data. Shown are changes in auditory and visual reaction times as a function of cocaine dose for both acute and chronic administrations. To make the data comparable to the acute cocaine data of Hienz et al. (1993), the present data were reanalyzed to represent the average of the minimum reaction time (lowest median reaction time to the high stimulus intensity) obtained during each session. Data points for saline were calculated in the same manner. These data show that both acute and chronic administration of cocaine produces similar dose–response effects for changes in reaction times, and that the chronic drug administration schedule may result in the same or only slightly greater decreases in reaction times than single cocaine injections do. Further, maximally shortened reaction times following chronic cocaine occurred within the dose

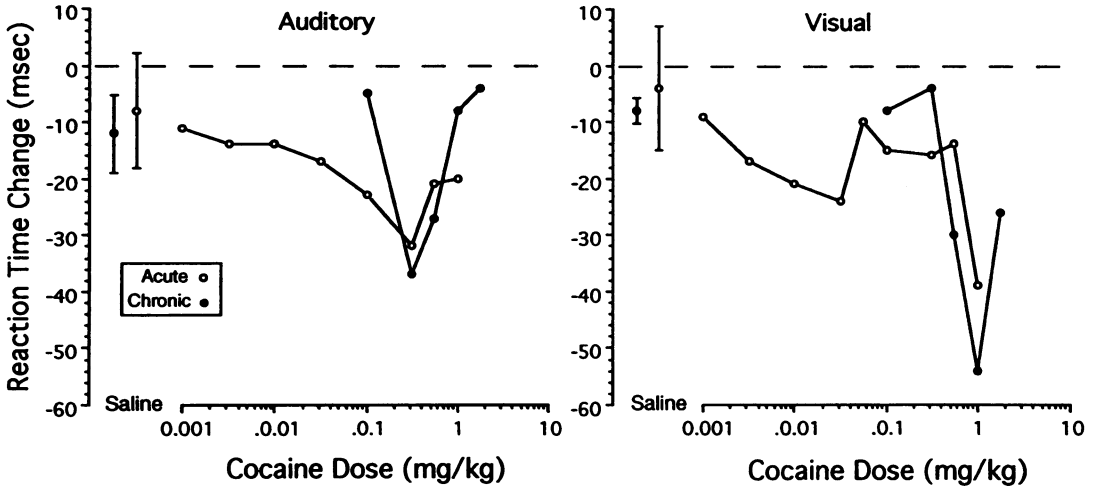

Fig. 9. Average changes in auditory (left) and visual (right) reaction times as a function of cocaine dose for both acute (open circles) and chronic (filled circles) administrations. The acute drug data are taken from Hienz et al. (1993). For all functions, each point represents the minimum reaction time (lowest median reaction time to the high stimulus intensity) obtained during each session averaged across all sessions and subjects. Error bars about saline points represent ±1.96 *SD* (95% confidence limits).

range of 0.32 to 1.0 mg/kg, resulting in a slightly U-shaped average dose–effect function. Based on the individual-animal data of Figure 1, this U-shaped function may be in part due to the averaging process across animals and different effective dose ranges. No major differences are apparent between cocaine's effects on auditory versus visual reaction times.

Sensitization to cocaine's stimulant effects (an increased responsiveness often indicated by a shift in the dose–effect function to the left) often occurs for "naturally occurring" behavior in a variety of species, including monkeys (Johanson & Fischman, 1989); for many operant performances, on the other hand, tolerance is often the more typical finding (e.g., Hoffman, Branch & Sizemore, 1987; Thompson, 1977). One of the more widely supported hypotheses concerning behavioral tolerance is that if a drug initially decreases reinforcement frequency for a behavior, tolerance is more likely to develop (Schuster, Dockens, & Woods, 1966). Based on this hypothesis, one would expect that cocaine's shortening of reaction times under the present procedures would not lead to the development of tolerance, because shortened reaction times would not result in decreased reinforcement frequency.

A second possible explanation for the observed shortened reaction times is that cocaine increases the sensitivity of organisms to sensory stimuli. In the present psychophysical procedures, shorter reaction times are often used as indices of more intense stimuli (e.g., "louder" tones or "brighter" light flashes), because reaction times normally vary inversely with stimulus intensity (Stebbins, 1966). Thus if the stimuli employed were functionally "louder" or "brighter" after cocaine administration, then shorter reaction times might be expected. Because no changes were observed in either auditory or visual thresholds, however, this explanation seems unlikely unless one further hypothesized that cocaine increased behavioral "reactivity" to stimuli in some manner in the absence of any sensory changes at or near threshold. In this regard, cocaine has been shown to produce a dose-related increase in the amplitude of the acoustic startle reflex in rats (Davis, 1985). A comparison of the effects of cocaine on acoustically elicited startle with its effects on electrically elicited startle has led to the suggestion that cocaine modulates neural activity relatively early in the startle reflex pathway, and that cocaine primarily affects the auditory sensory system rather than any motor output system in the reflex (Harty & Davis, 1985). Thus cocaine's effects in shortening reaction times could be due to a similar increase in responsiveness to acoustic stimuli. On the other hand, obvious problems with such a hy-

pothesis include the facts that (a) cocaine-induced changes in acoustic startle are primarily effects on the startle *amplitude* and not startle latency, and (b) in the present study, cocaine-induced shortenings of reaction time were observed with visual stimuli as well.

Although the present results suggest that daily cocaine administration does not affect behaviorally determined auditory threshold sensitivity, cocaine may affect other aspects of hearing, such as suprathreshold loudness functions. Abnormal increases in loudness (auditory "recruitment") are common in humans with a monaural hearing loss, and similar loudness effects have been demonstrated experimentally in monkeys using a reaction-time procedure (Pfingst et al., 1975). Following an experimentally induced hearing loss in one ear, for example, reaction times for tones in that ear show a rapid decrease at low intensities until the function "catches up" or reaches the normal asymptotic reaction-time levels at medium and higher intensities. The possibility of such loudness effects was examined in the present study by presenting 2 subjects with a series of stimuli over a wide range of stimulus intensities to determine the effects of cocaine over the extended reaction-time function. The results from Baboon MO indicated that cocaine shortened auditory reaction times for all intensities well above auditory threshold levels, a finding not consistent with the typical loudness recruitment phenomenon. Further, similar decreases in visual reaction times were observed with Baboon MU, suggesting that these effects are not specific to one sensory modality. Finally, the lack of convergence of Baboon MO's reaction-time functions for both cocaine and saline near threshold suggests an increased threshold sensitivity following cocaine (i.e., at threshold, reaction times following cocaine indicate a slightly "louder" stimulus than reaction times following saline); on the other hand, this animal's threshold estimates taken from psychometric functions showed no indications of increased sensitivity.

Cocaine administration produced pauses in responding that occurred typically at the beginning of the session and increased as a function of cocaine dose. At the highest cocaine doses, responding was so delayed that when animals began to respond, drug effects on reaction times were often negligible. This observation suggests that the increasing portion of the U-shaped dose–response function observed for reaction time in some animals may have been due to these lengthy pauses preventing an assessment of cocaine's effects on reaction times until after the effects had subsided. During these pause times, 2 subjects engaged in atypical behavior, but the remaining animals did not. Cocaine produced pausing in all animals, however, and no differences in pause times were observed to be related to the presence or absence of such atypical behavior. Similar dose-dependent pauses following cocaine were observed by Gonzales and Goldberg (1977) at the beginning of sessions with squirrel monkeys lever pressing under either a multiple fixed-interval (FI) fixed-ratio (FR) or a second-order FI (FR) schedule of reinforcement. Such pausing lasted for up to 60 min or more at the higher doses, following which schedule-typical response patterns were observed. In the present study, the increase in pausing diminished somewhat with continued daily cocaine administration for many subjects, suggesting the development of tolerance to the pause-increasing effects of cocaine. Further, long pauses during sessions substantially decreased the number of pellets received per session in the present study, and the observed tolerance would thus be consistent with the suggestion that behavioral tolerance may be observed when a drug alters behavior in such a way as to produce a decrease in the rate of reinforcement (e.g., see Schuster et al., 1966). Conversely, decreases in reaction times in the present study would not produce a decrease in the rate of pellet delivery, and no tolerance to such reaction-time effects were observed following cocaine.

There appear to be no studies in the literature that have directly examined cocaine's effects on either hearing or vision, but there are indications that such effects may exist. For example, cocaine users often experience hallucinations, with auditory hallucinations being most prominent (Brady, Lydiard, Malcolm, & Ballenger, 1991; Siegel, 1978). Cocaine can reduce the amplitude of some components of human auditory event-related potentials (Herning, Jones, Hooker, & Tulunay, 1985), although no changes in evoked potential sensitivity have been noted (Herning, Hooker, & Jones, 1987). In terms of visual function, it has been shown that *d*-methamphetamine can produce decrements in visual thresholds in

nonhuman primates (Hienz et al., 1985). Because cocaine and amphetamine have similar profiles of action, it has been suggested that at least some of cocaine's effects may be predicted from those known effects of amphetamine (Fischman, 1984). Given that no consistent changes in either auditory or visual threshold functions were observed in the present study, there do seem to be differences in the sensory threshold effects of cocaine and *d*-methamphetamine.

Although few data exist on cocaine's direct effects on sensory function, cocaine has been shown to affect performance accuracy in other types of discrimination procedures. Branch and Sizemore (1988), for example, found dose-related decreases in the rate of completing chains of complex response sequences and decreased performance accuracy during these chains in monkeys given acute administrations of cocaine; chronic administration of cocaine resulted in tolerance to both of these effects. On the other hand, cocaine has little effect on the accuracy of performing conditional visual discriminations in pigeons when stimulus control is high (Katz, 1990). In rats, cocaine has been reported to enhance accuracy on a vigilance task (Grilly & Grogan, 1990; Grilly & Nocjar, 1990). In humans, both impairments and improvements in discriminations have been reported following cocaine. In a repeated acquisition task, for example, low doses of cocaine given acutely did not affect accuracy, whereas high doses decreased accuracy (Fischman, 1984). On the other hand, cocaine has been reported to increase mood and arousal scores in humans (Foltin & Fischman, 1991) and to improve human performance in a digit symbol substitution test (Higgins et al., 1990).

The present data confirm previous data (Hienz et al., 1993) indicating that cocaine produces a variety of effects, including shortened reaction times in the absence of major changes in sensory threshold functions. The interpretation of such effects must proceed with caution; indeed, others have previously pointed to the often-perceived importance of the "edge" that stimulants may provide in highly practiced athletic performances (Laties & Weiss, 1981) as well as in other complex performances. It is unclear, however, whether similar changes in other performance measures might be observed following cocaine. Further, it is important to note that indications of cocaine-induced behavioral toxicity also occurred, because cocaine suppressed responding in a dose-dependent fashion, elevated reaction times in some animals, and produced abnormal behavior as well. Finally, it is not known whether or how different schedules of drug administration or interactions of cocaine with other drugs may affect such performances.

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